SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

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I. GENERAL INFORMATION

Product Generic Name:	Drug-Eluting Coronary Stent System (NIQ)
Product Trade Name:	TAXUS™ Express²™ Paclitaxel-Eluting Coronary Stent System (Monorail and Over-the-Wire)
Applicant's Name and Address:	Boston Scientific Corporation One Boston Scientific Place Natick, MA 01760
Premarket Approval Application (PMA) Number:	P030025
Date of Panel Recommendation:	November 20, 2003
Date of Notice of Approval to Applicant:	March 4, 2004

II. INDICATIONS FOR USE

The TAXUS™ Express²™ Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter for the treatment of de novo lesions ≤ 28mm in length in native coronary arteries ≥ 2.5 to ≤ 3.75 mm in diameter.

III. CONTRAINDICATIONS

Use of the TAXUS™ Express²™ Paclitaxel-Eluting Coronary Stent System is contraindicated in patients with:

- Known hypersensitivity to paclitaxel or structurally-related compounds.
- Known hypersensitivity to the polymer or its individual components (see details in **Section V – Product Description**, below)

Coronary Artery Stenting is contraindicated for use in:

- Patients in whom anti-platelet and/or anticoagulant therapy is contraindicated.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the TAXUS Express² Paclitaxel-Eluting Coronary Stent System labeling.

V. PRODUCT DESCRIPTION

The TAXUS Express² Stent System is a device / drug combination product comprised of two regulated components: a device (Express² Coronary Stent System) and a drug component (a formulation of paclitaxel contained in a polymer coating). The characteristics of the TAXUS Express² Stent System are described in **Table 1**.

Table 1. TAXUS Express² Stent System Product Description

	TAXUS Express² Monorail (MR) Stent Delivery System	**TAXUS Express²** Over-The-Wire (OTW) Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32	8, 12, 16, 20, 24, 28, 32
Available Stent Diameters (mm)	2.50, 2.75, 3.00, 3.50	2.50, 2.75, 3.00, 3.50
Stent Material	A 316L surgical grade stainless steel Express stent	
Drug Component	A conformal coating of a polymer carrier loaded with 1 μg/mm² paclitaxel in a slow release (SR)* formulation applied to the stent with a maximum nominal drug content of 209 μg on the largest stent (3.50x32mm).	
Delivery System Working Length	140 cm	135 cm
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤ 0.014".	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤ 0.014".
Stent Delivery Balloon	A compliant balloon, nominally 0.3 mm longer than the stent, with two radiopaque markers.	
Balloon Inflation Pressure	Nominal Inflation Pressure: 9 ATM; Rated Burst Inflation Pressure: 18 ATM	
Guide Catheter Inner Diameter	≥ 0.058"	≥ 0.066"
Catheter Shaft Outer Diameter	1.8F proximally, 2.7F distally (Ø up to 3.0mm, and 8-20 mm long stents with Ø > 3.0mm) 2.0F proximally, 2.7F distally (24-32mm long stents with Ø > 3.0mm)	3.2F proximally, 2.7F distally

* release rate is a function of weight/weight ratio of polymer and drug, and (SR) is the formulation that was studied clinically and is used in the marketed product

A. Device Component Description

The device component consists of the Express™ stent pre-mounted onto a stent delivery system (SDS); either the Express²™ Over-the-Wire (OTW) delivery system, or the Express²™ Monorail (MR) delivery system. The Express² OTW and MR delivery systems were previously approved for

deployment of the uncoated Express stent in P020009 (approved September 11, 2002).

The 2.5-3.5mm diameter 316L stainless steel stents use one design. The same stent is crimped on various size delivery catheter balloons, which are sized from 2.5 to 3.5mm. Because the identical stent component is used for the entire 2.5-3.5mm diameter range, the total drug per stent is a function of stent length, irrespective of stent diameter.

The Express^2 Delivery Catheters were not used in the pivotal clinical trial (TAXUS IV). The TAXUS IV trial used the Express Delivery Catheters. The only differences between the Express and the Express^2 versions of the delivery catheters are that: (1) the Express^2 catheter changed one of the shaft materials to another material that was used in other components of the original Express delivery catheter shaft; and (2) the Express^2 manifold was molded slightly differently to allow better retention in the packaging. This PMA requested approval of only the Express^2 OTW and MR delivery systems for use in delivering the TAXUS Express stent. Appropriate pre-clinical testing was provided to support the Express^2 stent delivery system, and acute (30 day) safety and performance data was submitted March 1, 2004 (TAXUS V trial, 1167 patients) to support the clinical safety of the TAXUS Express stent mounted on the Express^2 catheter design.

B. Drug Component Description

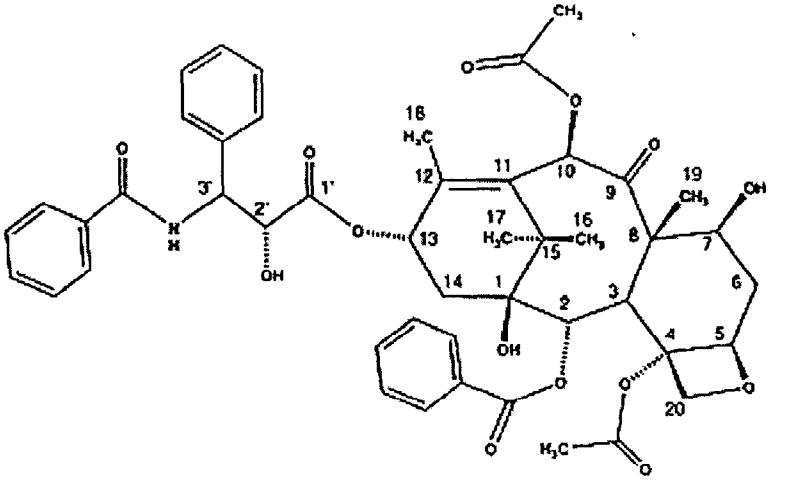
The drug component of the TAXUS Express^2 Paclitaxel-eluting Coronary Stent System (referred to as the TAXUS Express Stent) consists of paclitaxel (the active ingredient) and Translute™ polymer carrier (the inactive ingredient).

B1. Paclitaxel

The active pharmaceutical ingredient in the TAXUS Express Stent is paclitaxel. It is a white powder, isolated from a spectrum of Taxus species and hybrids. The Chemical name of paclitaxel is: Benzenepropanoic acid, β-(benzoylamino)-α-hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR-[2aα,4β,4aβ,6β,9α (αR*, βS*),11α,12α,12aα,12bα]]-.

The chemical structure of paclitaxel is shown below.

Figure 1. The Chemical Structure of Paclitaxel

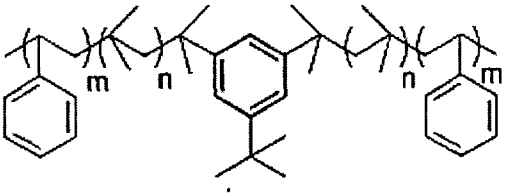


Paclitaxel is a diterpenoid with a characteristic taxane skeleton of 20 carbon atoms, a molecular weight of 853.91 g/mol and a molecular formula of C47H51NO14. It is highly lipophilic, insoluble in water, but freely soluble in methanol, ethanol, chloroform, ethyl acetate and dimethyl sulfoxide.

B2. Inactive Ingredients

The only inactive ingredient in the TAXUS Express stent is SIBS [poly(styrene-b-isobutylene-b-styrene)], a tri-block copolymer (trade name: Translute™), that is composed of styrene and isobutylene units built on 1,3-di(2-methoxy-2-propyl)-5-tert-butylbenzene. It is an hydrophobic elastomeric copolymer with a molecular weight (Mn-number average molecular weight) of 80,000 to 130,000 g/mol and a polydispersity index of 1.0 to 2.0. The polymer is mixed with the drug paclitaxel and then applied to the stents. There is no primer or topcoat layer. The drug/polymer coating is adhered to the entire surface (i.e., luminal and abluminal) of the stent. The structural formula for the polymer is shown below.

Figure 2. The Chemical Structure of SIBS [poly(styrene-b-isobutylene-b-styrene)]



m = repeating units of styrene
n = repeating units of isobutylene

Product Matrix and Paclitaxel Content

Table 2. TAXUS™ Express²™ Stent System Product Matrix and Paclitaxel Content

Product Code MR	Product Code OTW	Nominal Expanded Stent Inner Diameter (mm)	Nominal Un-expanded Stent Length (mm)	Nominal Paclitaxel Content (μg)
H7493897008250	H7493896808250	2.50	8	50
H7493897008270	H7493896808270	2.75	8	50
H7493897008300	H7493896808300	3.00	8	50
H7493897008350	H7493896808350	3.50	8	50
H7493897012250	H7493896812250	2.50	12	79
H7493897012270	H7493896812270	2.75	12	79
H7493897012300	H7493896812300	3.00	12	79
H7493897012350	H7493896812350	3.50	12	79
H7493897016250	H7493896816250	2.50	16	108
H7493897016270	H7493896816270	2.75	16	108
H7493897016300	H7493896816300	3.00	16	108
H7493897016350	H7493896816350	3.50	16	108
H7493897020250	H7493896820250	2.50	20	137
H7493897020270	H7493896820270	2.75	20	137
H7493897020300	H7493896820300	3.00	20	137
H7493897020350	H7493896820350	3.50	20	137
H7493897024250	H7493896824250	2.50	24	151
H7493897024270	H7493896824270	2.75	24	151
H7493897024300	H7493896824300	3.00	24	151
H7493897024350	H7493896824350	3.50	24	151
H7493897028270	H7493896828270	2.75	28	180
H7493897028300	H7493896828300	3.00	28	180
H7493897028350	H7493896828350	3.50	28	180
H7493897032270	H7493896832270	2.75	32	209
H7493897032300	H7493896832300	3.00	32	209
H7493897032350	H7493896832350	3.50	32	209

C. Mechanism of Action

The mechanism (or mechanisms) by which a TAXUS Express Stent affects neointimal production as seen in clinical studies has not been established. Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Treatment of patients with coronary artery disease may include exercise, diet, drug therapy, percutaneous coronary interventions (such as angioplasty, bare metal stents, coated stents, and other drug eluting stents), and coronary artery bypass surgery (CABG).

VII. MARKETING HISTORY

The TAXUS Express^2 Paclitaxel-Eluting Coronary Stent System is commercially available in the following countries:

- Argentina
- Austria
- Belgium
- Brazil
- Chile
- China
- Columbia
- Czech Rep.
- Denmark
- Egypt
- Finland
- France
- Germany
- Greece
- Hong Kong
- Hungary
- Iceland
- India
- Ireland
- Italy
- Jordan
- Liechtenstein
- Luxemburg
- Malaysia
- Mexico
- Netherlands
- Norway
- New Zealand
- Philippines
- Poland
- Portugal
- Singapore
- South Africa
- Spain
- Sweden
- Switzerland
- Thailand
- United Kingdom
- Uruguay

As of June 1, 2003, approximately 13,000 TAXUS Express Stents have been distributed outside of the U.S. No products have been withdrawn from the market in any country for any reason.

VIII. SUMMARY OF NON-CLINICAL STUDIES

A series of non-clinical laboratory studies were performed – those related to the stent and the stent delivery system [i.e., the stent mounted on either the Monorail (MR) or Over-the-Wire (OTW) stent delivery system (SDS)], the polymer substance [i.e., polyisobutylene styrene (SIBS)], the drug substance

(i.e., paclitaxel), and the finished combination product (i.e., TAXUS Express² paclitaxel-eluting coronary stent).

A. Biocompatibility Studies

A series of GLP and non-GLP biocompatibility tests and USP Physicochemical tests were conducted to demonstrate the components of the TAXUS Express² Paclitaxel-Eluting Coronary Stent System (Monorail and Over-the-Wire) are non-toxic. Tests were conducted on ethylene oxide-sterilized bare metal stents, stent delivery systems, polymer films, and polymer-only coated stainless steel (SS) coupons. These test articles were processed in the same manner as the finished TAXUS Express² product, except that where polymers were present (i.e., films and coupons), the drug substance, paclitaxel, was not included in the polymer coating. With the exception of the inclusion of the drug substance, the surface treatment, coating processing, amount of coating per unit area, and sterilization processes were equivalent for both the stents and coupons utilized during this testing. In all of these test systems, the materials were non-reactive and produced no greater response than the negative control employed in each test system.

All biocompatibility testing was conducted in accordance with:

- Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices; published by the Interventional Cardiology Devices Branch, Division of Cardiovascular, Respiratory and Neurology Devices, Office of Device Evaluation in May 1995.
- ISO 10993-1, Biological Evaluation of Medical Devices: Evaluation and Testing.

The GLP and non-GLP biocompatibility studies are summarized in **Table 3**.

Table 3. Biocompatibility Test Summary

Test Name	Test Description	Test Article and Results
Cytotoxicity	ISO 10993-5: In Vitro Cytotoxicity (L929 MEM Elution)	• Stent and delivery systems: Pass (non-cytotoxic) • Polymer-only coated 316L SS coupon: Pass (non-cytotoxic)
Sensitization	ISO 10993-10: Sensitization (Kligman Maximization)	• Stent and delivery systems: Pass (non-sensitizing) • Polymer-only coated 316L SS coupon: Pass (non-sensitizing)
Intracutaneous Reactivity	ISO 10993-10: Irritation (Injection)	• Stent and delivery systems: Pass (non-irritant) • Polymer-only coated 316L SS coupon: Pass (non-irritant)
Acute Systemic Toxicity	ISO 10993-11: Systemic Toxicity (Acute)	• Stent and delivery systems: Pass (non-toxic) • Polymer-only coated 316L SS coupon: Pass (non-toxic)

Test Name	Test Description	Test Article and Results
Pyrogenicity	LAL	▪ Stent and delivery systems: Pass (non-pyrogenic)
	ISO 10993-11: Systemic Toxicity (Material-Mediated Rabbit)	▪ Polymer-only coated 316L SS coupon: Pass (non-pyrogenic)
Hemocompatibility	Direct Contact Hemolysis	▪ Stent and delivery systems: Pass (non-hemolytic) ▪ Polymer-only coated 316L SS coupon: Pass (non-hemolytic)
	Lee and White Coagulation	▪ Stent and delivery systems: Pass (no change in coagulation time)
Implantation	14-Days (Rabbit, Intramuscular)	▪ Stent and delivery systems: Pass (non-toxic)
	30-Days (Rabbit, Intramuscular)	▪ Stent and delivery systems: Pass (non-toxic)
	14-Day Repeat Dose Subchronic Toxicity (Mouse, Intravenous)	▪ Stent and delivery systems: Pass (non-toxic)
	90-Day Chronic Toxicity (Mouse, Intraperitoneal)	▪ Polymer-only cast film: Pass (non-toxic)
Genotoxicity	Bacterial Reverse Mutation Assay (Ames Test)	▪ Polymer-only coated 316L SS coupon: Pass (non-mutagenic)
	In Vitro Chromosomal Aberration (human blood lymphocytes)	▪ Polymer-only cast film: Pass (non-clastogenic)
	In Vivo Mouse Micronucleus Test	▪ Polymer-only cast film: Pass (non-mutagenic)
Volatile/Metal Extracts	USP Physicochemical Extracts	▪ Stent and delivery systems: Pass

*Note: Express BMS & DES biocompatibility studies were conducted in accordance with GLPs. A rationale was provided for the non-GLP biocompatibility studies of Polymer-only coated SS/coupon and Polymer-only film studies to demonstrate that appropriate animal care procedures were followed, and data integrity was maintained.

Since the sponsor did not conduct the traditional battery of ISO-10993 testing on the finished TAXUS Express Stent (i.e., containing the drug substance), sub-chronic toxicity, thrombogenicity, and implantation of the final TAXUS Express product, containing all components and processing, were evaluated in porcine, rabbit, and canine models of stent-mediated vascular injury. The significant animal studies are summarized separately in **Section VIII F – Animal Studies** (below).

The genotoxicity, carcinogenicity, and reproductive toxicity of TAXUS Express Stents have not been evaluated. However, the genotoxicity, carcinogenicity, and reproductive toxicity of paclitaxel have been investigated in bacterial and mammalian cells *in vitro* and in laboratory animals *in vivo*.

Boston Scientific provided a letter from the drug substance manufacturer, Indena S.p.A., authorizing access to a Drug Master File (DMF) in support of this application. Indena manufactures a generic form of the drug Taxol®, a Bristol-Myers Squibb drug product that is approved for injection for multiple oncologic indications. *In vivo* animal and *in vitro* pharmacology and toxicology studies as well as *in vivo* and human pharmacokinetic studies were conducted on Taxol® to provide information

about systemic, regional and local toxicity, dose-related toxicity, distribution profiles, end-organ disposition, drug metabolism and potential drug-drug interactions.

There is no evidence to suggest that any chemical interactions occur, which would form a new intermediate or molecular entity, between paclitaxel or the polymeric carrier used in the TAXUS Express Stents.

Formal carcinogenicity testing on the final TAXUS Express Stent was not conducted. Because some paclitaxel remains on the product, and the carcinogenic potential of the SIBS polymer coating had not previously been investigated, an appropriate rationale was provided to demonstrate that the carcinogenic potential of the TAXUS Express Stent was minimal based on the types and quantities of starting materials (including any manufacturing additives).

Long term biocompatibility of the drug/polymer coating on the stent in humans is unknown.

B. *In Vivo* Pharmacokinetics

B1. TAXUS Express² Paclitaxel-Eluting Coronary Stent

In the clinical studies, TAXUS I, II, and III, no paclitaxel levels were detected after stent implantation using an analytical method with a lower limit of quantitation (LLOQ) of 10 ng/ml. These findings were confirmed in preclinical studies using multiple stents with total loaded doses above the clinically available stent system and an assay with an LLOQ of 0.03 ng/ml. Hence, in the absence of any systemically detectable levels, standard pharmacokinetic parameters were not estimated.

B2. Drug Interactions

Formal drug interaction studies have not been conducted with the TAXUS Express Stent. Paclitaxel is metabolized in the liver via cytochrome P450 (CYP) 2C8 to 6-alpha-hydroxypaclitaxel and via CYP 3A4 to 3'-p-hydroxypaclitaxel and 6-alpha,3'-p-dihydroxypaclitaxel. Paclitaxel is a substrate of P-glycoprotein. Because metabolism appears to play an important role in the elimination of paclitaxel, agents that could compete with or inhibit the CYP2C8 and CYP3A4 isoenzymes may increase paclitaxel plasma levels. Potential drug interactions may occur with any drug that affects these isoenzymes.

C. *In Vitro* Engineering Testing

In vitro engineering testing, in accordance with the FDA "Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents", May 1995, was conducted on the uncoated, bare versions of the Express stent mounted on either the Express or Express^2 MR and/or OTW delivery catheters, which were approved in P020009.

Supplementary *in vitro* engineering tests were also performed on the TAXUS Express Stent mounted on the Express and/or Express^2 delivery catheters. Some testing was not repeated since there was no change to the stent substrate, and where the effect of the coating and minor changes in design of the catheter delivery system were assumed to be negligible when evaluated against measurement and manufacturing tolerances. In tests that were repeated, values for the TAXUS Express stent were compared back to the uncoated stent as well as other bare metal coronary stents. Values reported for the products tested indicated statistical equivalence.

Additional tests were conducted to support the integrity of the coating on the TAXUS Express Stent and are summarized separately in **Section VIII D – Coating Characterization Testing**.

The *in vitro* engineering studies conducted are summarized in **Table 4**. "Pass" denotes that the test results met product specifications and/or the recommendations in the above-referenced guidance document.

Table 4: Stent and Delivery Catheter Engineering Testing

Test	Description of Test	Conclusion
Stent Material Specification Conformance Testing		
Bare Stent Material Analysis	Chemical analysis was conducted on the stainless steel ingot provided by the material supplier to confirm both chemical analysis and inclusion/impurity content as provided by ASTM F138-00 "Standard Specification for Wrought 18 Chromium-14 Nickel-2.5 Molybdenum Stainless Steel Bar and Wire for Surgical Implants (UNS S31673)."	Pass
Surface Contamination	The fully processed (but not sterilized) TAXUS Express stents were examined via SEM at 500X and 2000X to detect evidence of surface contamination or impurities on the stent material not removed by cleaning processes. Results of SEM evaluation showed no evidence of contamination above the specified limits.	Pass
Mechanical Properties: Tensile Strength & Elongation	Tensile strength and elongation testing was performed on tubing sizes used to fabricate the stents. The tensile strength and elongation met the product specifications.	Pass
Corrosion Resistance	As part of the fatigue testing, TAXUS stents were also tested according to ASTM F2129-01 "Standard Test Method for Conducting Cyclic Potentiodynamic Measurements to Determine the Corrosion Susceptibility of Small Implant Devices" to demonstrate that the finished stents exhibit corrosion and repassivation characteristics comparable to or	Pass

Test	Description of Test	Conclusion
	better than marketed 316L bare metal coronary stents. The results indicated that the corrosion resistance met product specifications.	
Stent Integrity Testing		
Metal to Artery Percentage	The metal surface coverage as a function of stent diameter was calculated by dividing the total vessel contact metal surface area of the stent structure by the surface area of the vessel at any given stent/vessel diameter. Metal to artery percentage ratios were calculated for all of the stent diameters recommended in the product labeling, with the highest surface to artery ratio (24.7%) occurring when the stent is deployed to the smallest diameter (2.5mm).	Pass
Length Changes Upon Expansion: Stent Foreshortening	The length of the stents were measured prior to and after expansion to the largest nominal diameter. All stents met product specifications.	Pass
Stent Expansion Uniformity	Testing was conducted to determine the uniformity of stent expansion along the stent length. Units were inflated to nominal diameters, deflated, and diameter measurements were taken at 3 points along the stent length. Measurements were averaged and compared to baseline measurements. All stents met the uniformity expansion specification.	Pass
Stent Recoil	Testing was conducted to quantify the amount of elastic recoil for the stent and correlate this parameter to the recommended sizing procedures. The system was inflated to nominal diameter and measurements were taken of the stent diameter at 3 locations along the stent. The system was then deflated and the same measurements taken. Results indicated that product specifications were met.	Pass
Stent Conformability Testing	Testing was conducted to determine the conformability (axial flexibility) of the stent in its expanded state by determining the pure bending moment of the stent. All diameter stents met specification.	Pass
Compression Resistance/Radial Hoop Strength	Testing was conducted to determine the radial resistance of the stent to external compression. All stents were expanded to nominal stent diameter, placed in a compression tester, forces were applied to compress the stent 0.5mm radially, and the forces were recorded. All stents met the compression resistance specifications.	Pass
Stent Expansion and Safety Margin	Testing was conducted to determine whether the deformation experienced by the stent undergoing expansion above the maximum rated diameter gives rise to stent or coating fractures. No stents exhibited any strut fractures or indications of coating integrity issues when visually examined at 32X following overexpansion.	Pass
Magnetic Resonance Imaging	Bench testing at field strengths of 3 Tesla (T) or less, and a maximum spatial gradient of 325 gauss/cm, showed that the stent should not migrate in this MR environment. This stent has not been evaluated to determine if it is safe in MRI systems with field strength greater than 3 T. The following statement is also included in the instructions for use: "This product has not been evaluated for heating in the MR environment. The effect of heating in the MR environment for overlapping stents or stents with fractured struts, or on the drug or polymer coating is not known. MR imaging quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent."	Pass
Stent Dimensional Verification	Testing was conducted to measure and optically inspect the stent to document that stent dimensional product specifications do not deviate from product specifications. All	Pass

Test	Description of Test	Conclusion
	product met specifications.	
Finite Element Analysis	An in-depth analysis of the stent was conducted to ensure that the implant conditions to which the stent will be subjected would not result in failure due to fatigue. The FEA evaluated the structural integrity of the stent and coating when subjected to the expected loading conditions generated in coronary arteries. The analysis took into account manufacturing, delivery, implantation and clinical loading over the implant life, and predicted that fatigue failures will not occur over the 400 million cycles of loading.	n/a
10 Year Accelerated Pulsatile Fatigue Testing	Accelerated *In vitro* testing of approximately 10 years (400 million cycles) equivalent real time was conducted to ensure that the stent, when expanded to its largest intended diameters, will not show fatigue failure during simulated 10 year life span testing. The stents were dynamically cycled over simulated vessel conditions for 400 million cycles. Following cycling, stents were visually inspected using 40X optical microscopy. No signs of strut cracking or breaking were detected. Additionally, eight stents (4 coated, and 4 with coating removed after fatigue testing) were randomly analyzed using SEM. All tested stents were free from fatigue induced surface defects, and there was no evidence of coating fatigue or corrosion. The stent met the 10 year accelerated fatigue resistance requirement of the product specification.	Pass
Stent Radiopacity	Testing was conducted on the bare metal stent as the addition of the coating did not add or detract from the radiopacity of the stent in clinical use.	Pass
Stent/Catheter Delivery System Testing		
Balloon in Stent Burst, Balloon Bonds, and Inflation Lumen Integrity Testing	Stents systems with sizes representative of the available product were tested to burst, and all other sizes were also tested and required to meet rated burst pressure. All stent systems met rated burst pressure. The results demonstrate with 95% confidence that at least 99.9% of the balloons will not experience loss of integrity at or below the rated burst pressure.	Pass
Stent Diameter vs. Balloon Inflation Pressure (Compliance)	Testing was performed to determine how the diameter of a deployed balloon varies with applied balloon pressures. The stent sizing results verify that the stent systems meet the labeled compliance values.	Pass
Stent Deployment Testing	Testing was performed to determine the TAXUS Express and Express² stent deployment pressures. Samples of every TAXUS Express stent and delivery system and representative sizes of the TAXUS Express² stent and delivery system were tested and demonstrated that these product met the labeled deployment specification of $\leq$ 9 atm (132 psi).	Pass
Balloon Inflation and Deflation Testing	Express² delivery systems across the range of balloon lengths and diameters were tested for inflation/deflation times, and all stent systems met specifications.	Pass
Repeat Balloon Inflation	TAXUS Express² stent systems across the range of stent/balloon lengths and diameters were required to complete 20 pressurization cycles to Rated Burst Pressure (RBP). The stent/balloon burst results show statistically that, with 95% confidence, 90% of the catheters will not experience balloon, shaft, or proximal/distal seal loss of integrity at or below the maximum recommended rated balloon burst pressure.	Pass
Stent/Balloon Crossing Profile	Stent systems for each diameter balloon were tested to determine the deflated stent/balloon profile. All samples met the product specification.	Pass

Test	Description of Test	Conclusion
Pre- and Post-Deployment Catheter Withdrawal Forces (into a Guide Catheter)	Testing was carried out to verify that the TAXUS Express² Stent system can be safely withdrawn back into the recommended guide catheter sizes both before and after stent deployment. This testing also verified that after stent deployment, the balloon could be withdrawn from the stent. Testing indicated that all samples could be withdrawn back into the recommended guide catheter prior to and after stent delivery. All samples met the product specification.	Pass
Non-Coaxial Withdrawal Forces (into a Guide Catheter)	Testing was carried out to demonstrate that the TAXUS Express2 stent system can be safely withdrawn into the guide catheter when the entry is non-coaxial. Testing indicated that all samples could be withdrawn back into the recommended guide catheter after tracking through a simulated tortuous model. All samples met the product specification.	Pass
Stent Securement - Force Testing	Testing was conducted to assess the force required to displace a crimped TAXUS stent from the Express² delivery systems (1) directly from the balloon catheter, and (2) after tracking through a simulated tortuous artery model. All stent systems met the stent securement specification. Stent securement to the specification was demonstrated with 95% confidence that 99.7% of the TAXUS Express stents will not be dislodged from the Express² delivery systems.	Pass
System Track Testing	Testing was conducted to demonstrate that the tracking force of the TAXUS Exress² Coronary Stent System through a simulated artery is comparable to the Express Coronary Stent System. Peak force was measured as the catheter was tracked through a simulated artery, and found to be comparable. All samples met product specification.	Pass
Full Unit Tensile Testing	Representative sizes of the TAXUS Express² stent delivery system were tested to determine the tensile strength of the delivery catheter. All stent systems exceeded the minimum catheter tensile strength specification.	Pass

D. Coating Characterization Testing

The following methods were developed to characterize and set initial specifications for the TAXUS Express stent. The coating characterization testing conducted on the TAXUS Express stent is summarized in **Table 5**.

Table 5: Coating Characterization Testing

Test	Description of Test
Materials Analysis - Polymer	Polymer components were tested to ensure conformity to raw material specifications and incoming inspection procedures.
Chemical Analysis – Polymer	Assays were conducted to determine Mw, Mn, polydispersity, monomer content, presence/formation of oligomers and free monomers.
Chemical Analysis - Drug	Drug substance was tested to ensure conformity to incoming Certificate of Analysis.
Drug Content	Assay was conducted to quantitatively determine the total amount of the drug substance, paclitaxel, on the TAXUS Express stent.
Dose Density	Dose per unit area was calculated.
Drug Content along Stent Length	Testing was conducted to characterize the uniform distribution of drug along the length of the TAXUS Express stent.
Coating Uniformity/ Reproducibility	Testing was conducted to verify the reproducibility of coating uniformity from stent to stent and batch to batch.
Coating Thickness	Testing was conducted to describe the coating thickness along the length of the stent.

Test	Description of Test
Impurities/Degradation Products	Assays were conducted to quantitatively determine the type and amount of impurities and degradation products on the TAXUS Express stent.
In Vitro Elution	Assay was developed to measure the *in vitro* release kinetics of paclitaxel off the TAXUS Express stent.
Particulates	Particulate levels were determined for the TAXUS Express² stent delivery system (pre- and post-deployment) to be within the USP <788> specification for small volume injections.

E. Chemistry Manufacturing and Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) Guidelines were followed for the testing routinely performed on the TAXUS Express² stent as part of CMC. This testing is summarized in **Table 6**. Information to support the stability of the TAXUS Express² Stent is summarized separately in **Section VIII G – Stability**, below.

Table 6: CMC Release Testing

Test	Description of Test
Material Analysis – Polymer	The polymer was tested to ensure conformity to specifications. The polymer met specifications prior to utilization in finished goods.
Drug Identity	Assay was conducted to verify the identity of the drug substance, paclitaxel, on the TAXUS Express stent. The product met specifications established for finished goods release.
Drug Content/Impurities	Assays were conducted to quantitatively verify the amount of drug and the type and amount of impurities on the TAXUS Express stent. The product met specifications established for finished goods release.
Drug Content Uniformity	Multiple stents were assayed to verify the uniformity of the drug content between individual stents was within specifications established for finished goods release.
Residual Solvents	Assay was conducted on the TAXUS Express stent to verify that residual levels of solvents used in the manufacturing process were below acceptable limits established for finished goods release.
In Vitro Elution	The *in vitro* release profile of paclitaxel was measured on the TAXUS Express stent. Specifications were based on the elution characteristics of stents evaluated in the clinical investigation. The product met specifications established for finished goods release.
Particulates	Particulate levels were monitored to verify that they remain below acceptable levels as established in the product specifications.

F. Animal Studies

Detailed arterial histopathology and histomorphometry are not obtainable through human clinical trials, so a series of animal studies were conducted to evaluate safety, efficacy (proof of concept), and overall product performance.

Boston Scientific conducted a series of studies evaluating a variety of paclitaxel-eluting stent formulations (e.g., various drug dosages and concentrations, etc.), polymer-coated control stents and/or bare metal control stents. These studies were conducted in coronary arteries of pigs,

or iliac arteries of rabbits. These studies served as the basis for the dose selection for the TAXUS Express stent used in the clinical studies.

The intravascular safety and biocompatibility of paclitaxel-eluting stents were evaluated in a series of animal studies in a porcine model of stent-mediated vascular injury. Some of these studies were conducted in accordance with §21CFR 58 (Good Laboratory Practices). A rationale was provided for the non-GLP animal studies to demonstrate that appropriate animal care procedures were followed, and data integrity was maintained. The results of these tests support the safety and biocompatibility of the TAXUS Express Stent. Summaries of these studies are included in **Table 7**.

Table 7: Summary of Major Supportive Animal Studies

Study #	Stent Design	Type/ # of Animals	# of Stents	Follow-up Duration	Endpoints
BS5P	Test Article: TAXUS Express Stent MR* (3.0x8mm, 3.5x8mm) Control: BMS GLP: no	Domestic Swine Test & Control: 36 (LAD, LCX, RCA) 2 stents/vessel Animals received both test and control	Test: 54 Control: 34	28, 90, & 180 days	• Histologic and histomorphometric evaluations of overlapping stents • Evaluation of degree of re-endothelialization by SEM • Acute delivery • Chronic vascular response.
RVF 02-069	TAXUS Express SR** (3.0x16mm, 3.5mmx16mm) Control: BMS GLP: no	Domestic Swine Test & Control: 11 (LAD, LCX, RCA) 2 stents/vessel Some animals received both test and control	Test: 16 Control: 18	180 days	• Histologic and histomorphometric evaluations of overlapping stents • Evaluation of degree of re-endothelialization by SEM • Chronic vascular response
A242-GX-00	Test Article: polymer- coated NIR Conformer (no drug) [3.0x15mm, 3.5mmx15mm] Control: BMS GLP: no	Domestic Swine Test: 14 Control: 13 (LAD, LCX, RCA) 1 stent/vessel	Test: 26 Control: 22	28, 90, & 180 days	• Histologic and histomorphometric evaluations • Chronic vascular response (SIBS polymer coating & BMS)
RVF01-049 and 050	TAXUS Express MR (3.0x16mm, 3.5x16mm) Control: BMS GLP: Yes	Domestic Swine Test: 23 Control: 22 (LAD, LCX, RCA) 1 stent/vessel 1 or 2 stents/animal	Test: 35 Control: 35	28, 90, 180, & 360 days	• Histologic and histomorphometric evaluations of overlapping stents • Evaluation of degree of re-endothelialization by SEM • Acute Delivery • Chronic vascular response
A203-GX-00	TAXUS NIRx MR (3.0x15mm, 3.5x15mm) GLP: yes	Domestic Swine Test: 17 Control: 15	Test: 38 Control: 30	28, 90, & 180 days	• Histologic and histomorphometric evaluations of overlapping stents • Evaluation of degree of

Study #	Stent Design	Type/ # of Animals	# of Stents	Follow-up Duration	Endpoints
					re-endothelialization by SEM • Chronic vascular response

*MR = Moderate Release formulation of TAXUS Express stent (not the subject of this PMA application)
**SR = Slow Release formulation of TAXUS Express stent (the subject of this PMA application)

G. Stability

Site-specific stability studies were conducted to establish a shelf life/expiration date for the TAXUS Express^2 Paclitaxel-Eluting Coronary Stent System. Testing to establish package integrity and functional testing of the stent system were conducted on aged product. Testing evaluation included drug identity, assay, degradants, *in vitro* elution, particulates, sterility, drug content uniformity, residual solvents and endotoxins. Appropriate engineering tests were also repeated on aged product and compared to baseline to ensure that the TAXUS Express^2 Stent System performed acceptably. The data generated support a shelf life of 6 months.

A GLP polymer stability study was conducted to establish the chemical stability of the main inactive ingredient in the TAXUS Express stent. The stability of SIBS was investigated via GPC analysis of explanted cast polymer films that had been implanted for 13 weeks in a mouse model, with no change in molecular weight or polydispersity. In addition, a literature review was conducted to support that chemical degradation of this polymer is unlikely to occur in the physiologic environment.

H. Sterilization

The TAXUS Express^2 Paclitaxel Eluting Stent System (Monorail and Over-The-Wire) is sterilized using ethylene oxide sterilization, and has been validated per AAMI/ISO 11135:1994 "Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization."

Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}.

The amount of bacterial endotoxins was verified to be within the specification limit for TAXUS Express^2 stent delivery systems.

IX. OVERVIEW OF CLINICAL STUDIES

TAXUS IV was a randomized, double-blind, controlled pivotal U.S. study of the safety and performance of the 1 µg /mm^2 (loaded drug/stent surface area) slow rate-release formulation TAXUS™ Express™ Stent in patients with low risk, *de novo* coronary artery lesions. A total of 1,326 patients at 73 U.S. sites were enrolled with patients randomized 1:1 to the TAXUS Express Stent or the uncoated Express control stent. The primary endpoint for the study was the 9-month ischemia driven TVR rate. Secondary endpoints included 9-month clinical assessments for all patients and analysis of angiographic and intravascular ultrasound (IVUS) parameters in a subset of patients. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 6 months. Follow-up through 12 months is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

TAXUS II was a randomized, double-blind, controlled supporting study of the safety and performance of the 1 µg/mm^2 TAXUS NIRx™ Paclitaxel-Eluting Coronary Stent System (TAXUS NIRx Stent), in which two sequential cohorts of patients with low risk, *de novo* coronary artery lesions were treated. The slow rate-release (SR) formulation was studied in Cohort I and the moderate rate-release (MR) formulation in Cohort II. A total of 536 patients in 15 countries were enrolled. Patients in each cohort were randomized (1:1) to the TAXUS NIRx Stent or the NIR™ Conformer uncoated control stent. The primary endpoint for the study was mean percent in-stent net volume obstruction at 6 months as measured by IVUS. Secondary endpoints included 6-month clinical and angiographic parameters. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 6 months. Follow-up through 12 months is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing, with an additional angiographic follow-up scheduled at the 2 year time-point. For TAXUS II, results are only presented for the SR treatment group (Cohort I) and corresponding control.

TAXUS I was a randomized, double-blind, controlled feasibility study comparing the 1 µg /mm^2 slow rate-release formulation of the TAXUS NIRx Stent with the NIR Conformer uncoated control stent in *de novo* lesions. IVUS guidance during the index procedure and at 6-month follow up was required. Patients received aspirin indefinitely and clopidogrel or ticlopidine for 6 months. In brief, 61 patients were enrolled by 3 centers in Germany. Baseline demographic, lesion characteristics were similar between the 2 groups. The primary endpoint was 30-Day Major Adverse Cardiac Event (MACE). Follow-up through 24 months is currently available and follow-up for clinical parameters through 5 years is ongoing.

Table 8. Clinical Trial Comparison

	TAXUS IV (Pivotal)	TAXUS II (SR) (Supportive)	TAXUS I (Feasibility)
Study Type	• prospective • multi-center randomized • double-blind	• prospective • multi-center randomized • double-blind • two sequential cohorts	• prospective • multi-center randomized • double-blind
Number of Patients	Total: 1314 TAXUS Express Stent: 662 Control: 652	Total: 267 TAXUS NIRx Stent: 131 Control: 136	Total: 61 TAXUS NIRx Stent: 31 Control: 30
Dose Release Formulation	SR (1 µg /mm^2)	SR (1 µg /mm^2)	SR (1 µg /mm^2)
Lesion Criteria	*De novo* lesions in native coronary artery ≥10mm and ≤28mm in length and vessel diameter ≥ 2.5mm to ≤ 3.75mm in diameter and coverable with 1 stent	*De novo* lesions in native coronary artery ≤ 12mm in length and vessel diameter ≥ 3.0mm to ≤ 3.5mm in diameter and coverable with 1 stent	*De novo* lesions in native coronary artery ≤ 12mm in length and vessel diameter ≥ 3.0mm to ≤ 3.5mm in diameter and coverable with 1 stent
Product Used	Express Stent on the Maverick™ Monorail Stent Delivery Balloon Catheter	NIRx Stent premounted on the Advance Monorail Stent Delivery Balloon Catheter	NIRx Stent hand-crimped on the Advance Monorail Stent Delivery Balloon Catheter
Antiplatelet Therapy	Aspirin indefinitely and clopidogrel or ticlopidine for 6 months	Aspirin indefinitely and clopidogrel or ticlopidine for 6 months	Aspirin indefinitely and clopidogrel or ticlopidine for 6 months
Follow-Up	30 days: clinical 4 months: clinical or telephone 9 month: clinical, angiographic 1 – 5 years: telephone	30 days: clinical 6 and 24 months: clinical, angiographic 1,3,4,5 years: telephone	30 days: clinical 6 and 24 months: clinical, angiographic 1,3,4,5 years: telephone

X. POTENTIAL ADVERSE EFFECTS OF THE PRODUCT ON HEALTH

A. Observed Adverse Events

Observed adverse event experience comes from three clinical studies, TAXUS IV, II and I.

Principal adverse events for these trials are shown in **Table 9.** Stent apposition was recorded for the TAXUS IV and TAXUS II trials and is presented in **Table 9**. See also **Section X B - Potential Adverse Events**, below.

Table 9. Principal Adverse Events

	TAXUS IV (SR) to 12 months		TAXUS II (SR) to 12 months		TAXUS I (SR) to 24 Months	
	TAXUS Stent	Control Stent	TAXUS Stent	Control Stent	TAXUS Stent	Control Stent
In-Hospital	N=662* % (n)	N=652* % (n)	N=131* % (n)	N=136* % (n)	N=31* % (n)	N=30* % (n)
MACE	2.4% (16)	2.1% (14)	1.5% (2)	4.4% (6)	0.0% (0)	0.0% (0)
Death	0.0% (0)	0.3% (2)	0.0% (0)	0.7% (1)	0.0% (0)	0.0% (0)
Myocardial Infarction	2.4% (16)	2.1% (14)	1.5% (2)	3.7% (5)	0.0% (0)	0.0% (0)
Q-wave	0.2% (1)	0.2% (1)	0.0% (0)	0.7% (1)	0.0% (0)	0.0% (0)
Non Q-wave	2.3% (15)	2.0% (13)	1.5% (2)	2.9% (4)	0.0% (0)	0.0% (0)
Target Vessel Revascularization (TVR)	0.0% (0)	0.2% (1)	0.8% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Target Lesion Revascularization (TLR)	0.0% (0)	0.2% (1)	0.8% (1)	0.0% (0)	0.0% (0)	0.0% (0)
TVR, non-target lesion	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
TVR, CABG	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
CVA	0.0% (0)	0.2% (1)	0.0% (0)	0.0% (0)	-	-
Stent Thrombosis (acute/in-hospital)	0.0% (0)	0.3% (2)	0.8% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Out-of-Hospital	N=653* % (n)	N=644* % (n)	N=129* % (n)	N=131* % (n)	N=31* % (n)	N=30* % (n)
MACE	8.4% (55)	18.3% (118)	9.3% (12)	18.3% (24)	3.2% (1)	10.0% (3)
Death	1.4% (9)	0.9% (6)	0.0% (0)	0.8% (1)	0.0% (0)	0.0% (0)
Myocardial Infarction	1.1% (7)	2.5% (16)	0.8% (1)	2.3% (3)	0.0% (0)	0.0% (0)
Q-wave	0.6% (4)	0.2% (1)	0.8% (1)	1.5% (2)	0.0% (0)	0.0% (0)
Non Q-wave	0.5%% (3)	2.3% (15)	0.0% (0)	0.8% (1)	0.0% (0)	0.0% (0)
Target Vessel Revascularization (TVR)	6.9% (45)	16.8% (108)	9.3% (12)	16.0% (21)	3.2% (1)	10.0% (3)
Target Lesion Revascularization (TLR)	4.3% (28)	14.8% (95)	3.9% (5)	13.0% (17)	0.0% (0)	10.0% (3)
TVR, non-target lesion	2.8% (18)	3.1% (20)	3.1% (4)	3.1% (4)	3.2% (1)	0.0% (0)
TVR, CABG	1.7% (11)	4.0% (26)	3.1% (4)	0.8% (1)	0.0% (0)	3.3% (1)
CVA	1.7% (11/654)	0.6% (4)	0.8% (1)†	0% (0/136)	-	-
Stent Thrombosis (sub-acute/<30 days)	0.3% (2)	0.3% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Stent Thrombosis (late/≥31 days)	0.3% (2)	0.2% (1)	0.8% (1)	0.0% (0)	0.0% (0)	0.0% (0)

Numbers are % (Count/Sample Size). * Note: sample size is defined as N at the top of each column for In-Hospital and Out-of-Hospital measures except where noted by inclusion of a denominator

MACE: Major Adverse Cardiac Events, comprised of Cardiac Death, MI and TVR.

TVR: Target Vessel Revascularization, defined as Ischemia-driven repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel. A TVR will be considered as ischemia-driven if the target vessel diameter stenosis is ≥50% by QCA and any of the following are present:

- the patient had a positive functional study corresponding to the area served by the target vessel;
- ischemic ECG changes at rest in a distribution consistent with the target vessel;
- ischemic symptoms referable to the target lesion.

Primary endpoint of TAXUS IV: 9-month TVR.

For definitions of other AEs refer to tables 9-1 and 9-2

†This event was reported by site as Serious Adverse Event (SAE) (visual field defect right eye): It was subsequently adjudicated by the Clinical Event Committee as a Transient Ischemic Attack but downgraded to the non-serious adverse event.

In the TAXUS IV trial, a pre-specified subset of patients underwent IVUS evaluation of the treated lesion immediately after treatment and as part of a scheduled angiographic evaluation at 9 months. In the TAXUS II trial, all patients underwent IVUS evaluation immediately after treatment and as part of the follow-up angiographic evaluation at 6 months. In both studies, the incomplete apposition rate post-procedure and at follow-up was comparable between patients in the TAXUS stent treatment group and the Control group. From the TAXUS IV trial, the majority of incomplete stent apposition cases that were present post-procedure had resolved, and the incidence of late acquired stent apposition was low and comparable between groups. There was no correlation of clinical adverse events or MACE events that were related to the occurrence of incomplete stent apposition. Frequencies of incomplete stent apposition are shown in **Table 10** for both TAXUS IV and TAXUS II.

Table 10. Frequency of Incomplete Stent Apposition

	TAXUS IV (SR) Trial		TAXUS II (SR) Trial	
	TAXUS Stent	Control Stent	TAXUS Stent	Control Stent
Incomplete Stent Apposition Rate Post-Procedure	11.6% (13/112)	6.4% (7/109)	11.1% (14/126)	9.3% (12/129)
Incomplete Stent Apposition Rate at Follow-up	4.0% (4/99)	3.0% (3/100)	12.5% (15/120)	7.9% (10/127)
Resolved	6.4% (6/94)	5.4% (5/93)	6.8% (8/118)	4.9% (6/123)
Persistent	3.2% (3/94)	1.1% (1/93)	4.2% (5/118)	4.1% (5/123)
Late Acquired	1.1% (1/94)	2.2% (2/93)	8.5% (10/118)	4.1% (5/123)

Numbers are % (Count/Sample Size).
IA = Incomplete Apposition, BL = Baseline, FU = Follow-up.
Resolved = # patients with BL IA and without FU IA ÷ # patients evaluable at baseline and follow-up.
Persistent = # patients with BL IA and with FU IA ÷ # patients evaluable at baseline and follow-up.
Late Acquired = # patients without BL IA and with FU IA ÷ # patients evaluable at baseline and follow-up.
Incomplete Apposition variables are from assessment by IVUS core laboratory.

B. Potential Adverse Events

Potential adverse events (in alphabetical order) which may be associated with the use of a coronary stent in native coronary arteries include but are not limited to:

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction
- Aneurysm
- Angina
- Arrhythmias, including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous fistula
- Cardiac tamponade
- Coronary Artery Occlusion
- Cardiogenic shock

- Death
- Dissection
- Drug reactions to antiplatelet agents / anticoagulation agents / contrast media
- Emboli, distal (air, tissue or thrombotic emboli)
- Embolization, stent
- Emergent Coronary Artery Bypass Surgery (CABG)
- Failure to deliver the stent to the intended site
- Fever
- Fistulization
- Heart failure
- Hematoma
- Hemorrhage
- Hypotension/Hypertension
- Incomplete Stent Apposition
- Infection, including infection and/or pain at the access site
- Myocardial infarction
- Myocardial ischemia
- Perforation or Rupture
- Pericardial effusion
- Prolonged angina
- Pseudoaneurysm
- Renal failure
- Respiratory Failure
- Restenosis of stented segment
- Rupture of native and bypass graft
- Shock/Pulmonary edema
- Spasm
- Stent compression
- Stent migration
- Stroke/cerebrovascular accident/TIA
- Stent thrombosis (acute, subacute, or late)/occlusion
- Ventricular fibrillation
- Vessel perforation
- Vessel spasm
- Vessel trauma requiring surgical repair or reintervention

Potential adverse events not captured above, that may be unique to the paclitaxel drug coating:

- Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds) or the polymer stent coating (or its individual components)
- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms

- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- Myalgia/Arthralgia
- Peripheral neuropathy

There may be other potential adverse events that are unforeseen at this time.

XI. SUMMARY OF CLINICAL STUDIES

A. TAXUS IV Pivotal Clinical Trial

Objective: The primary objective of this study was to demonstrate superiority of the TAXUS™ Express™ Stent as compared with a matched uncoated control stent for reduction of the target vessel revascularization rate (TVR) 9 months post index procedure.

Conclusion: In selected patients, the TAXUS Express Stent significantly reduced the rate of 9-month TVR (primary endpoint) as compared to control. This reduction was attributable to reduction in revascularization procedures [percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)] performed on the target lesion (TLR). Quantitative coronary angiography (QCA) and IVUS analyses confirmed a significant reduction in binary restenosis rate, minimum lumen diameter (MLD), percent diameter stenosis (%DS), late loss, and % in-stent net volume obstruction. These results were achieved without increased edge stenosis and late loss at the proximal and distal edges, which were significantly lower in the TAXUS group. In addition, lower MACE rates in the TAXUS group, along with low and comparable rates of stent thrombosis, aneurysm and incomplete apposition between groups, demonstrates the safety of the TAXUS Express Stent.

Design: This was a multi-center, prospective, randomized, double-blind study in patients at 73 U.S. sites. Eligible patients were those presenting for stenting of de novo lesions of a single native coronary artery [reference vessel diameter (RVD) 2.5 to 3.75 mm] with a target lesion 10 to 28 mm in length and stenosis ≥50% in diameter, using visual estimates, who were candidates for PCI or CABG, and had documented angina pectoris or functional ischemia.

A total of 1314 patients were enrolled and evaluable in this study: 662 in the TAXUS group and 652 in the Control group. Patients were randomized to receive either a TAXUS Express Stent or uncoated Express™ coronary stent (bare metal control). Study randomization was sub-stratified for medically

treated diabetes, reference vessel diameter, and lesion length. Multiple stenting was allowed for bailout only. After the procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for 6 months.

Follow-up included 1, 4, and 9-month clinical assessments. In addition, patients agreed to annual telephone follow-up for clinical parameters through 5 years post procedure (Note: 4-month follow-up was by phone or office visit). Follow-up through 12 months (+ 30 days) is currently available in 1272/1314 (96.8%) of patients.

A subset of patients were pre-assigned to have angiographic (n=732) and IVUS (n=268) follow-up at 9 months. Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and also for the area within the stent margins, including the area immediately 5 mm proximal and distal from the stent margins (analysis segment).

Demographics: Patients were well matched for baseline demographics with no statistically significant differences between groups. Factors evaluated included age (mean 62 years), gender (72% male), race (89.3% Caucasian, 5.0% African American, 3.1% Hispanic, 1.6% Asian, and approximately 1.0% other), diabetes (29%), prior MI (30%), hypertension (70%), hyperlipidemia (65%), ejection fraction (mean 55%), Canadian Cardiovascular Society Classification (CSS) Angina Class (26% III or IV), IIb/IIIa inhibitor use (57%), left anterior descending (LAD) (41%), left circumflex (LCX) (28%), right coronary artery (RCA) (31%), RVD (mean 2.8 mm), MLD (mean 0.93 mm), %DS (mean 66%), and lesion length (mean 13.4 mm). Smoking history (current and previous) was slightly lower in the TAXUS™ Express™ Stent arm (63.0%) than in the control arm (66.3%), and was not found to be a significant predictor of outcome in the trial.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by coordinators at the clinical sites. Angiographic and IVUS outcomes were assessed in a blinded fashion by quantitative analysis at designated core laboratories. An independent Clinical Events Committee adjudicated clinical events, and the trial was monitored by an independent Data Monitoring Committee.

Results: In selected patients, elective TAXUS Express Stent placement in native coronary artery de novo lesions resulted in a reduction in the incidence of TVR at 9 months compared to Control (4.7% vs. 12.1%, $p<0.0001$). Overall MACE including cardiac death, myocardial infarction (MI) and target vessel revascularization (TVR) were reduced in the TAXUS group at 9 months compared to control (8.5% vs. 15.2% , $p= 0.0002$). Stent thrombosis rates were comparable between the groups (0.6% TAXUS vs 0.8% Control, $p=0.7513$). Clinical outcomes through 12 months were consistent with the 9 month outcomes.

By follow-up angiography at 9 months, there was a significantly lower in-stent late loss (0.39 mm vs. 0.92 mm, p<0.0001) and analysis segment late loss (0.23 mm vs. 0.61 mm, p<0.0001) as compared to Control. Additionally, in-stent and analysis segment binary restenosis were significantly reduced (5.5% vs. 24.4%, p<0.0001, in-stent; 7.9% vs. 26.6%, p<0.0001, analysis segment). Percent diameter stenosis and late loss at the proximal (13.19% vs. 16.13%, p=0.0167; 0.15 mm vs. 0.27 mm, p=0.0016) and distal edges (7.60% vs. 11.83%, p=0.0001; 0.05 mm vs. 0.17 mm, p=0.0007) were significantly lower in the TAXUS as compared to the Control groups.

Examination by IVUS at 9 months showed that neointimal hyperplasia volume was significantly reduced in the TAXUS Express Stent arm (17.56 mm3 vs. 41.48 mm3, p<0.0001). The rate of incomplete stent apposition was low and comparable between the TAXUS and Control treatment arms at 9-months (4.0% vs. 3.0%, p=0.7209). There were no clinical events related to occurrences of incomplete stent apposition.

Forty-two (6.5 %) of the patients in the TAXUS Express Stent arm of the TAXUS IV trial received more than one stent for bailout purposes. The incidence of MACE in these patients was not different than in those patients receiving only one stent.

Table 11 summarizes principal safety and effectiveness results through 12 months and **Figure 3** provides the cumulative percent of patients who are TVR-Free through 12 months.

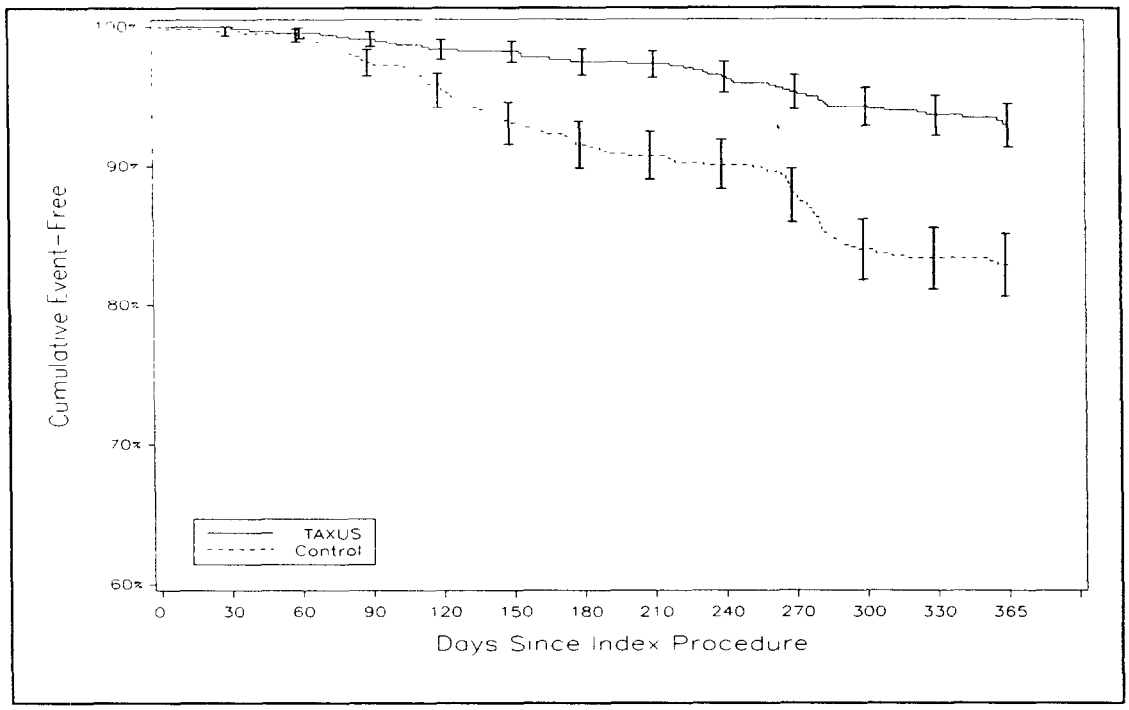
Table 11.TAXUS IV Principal Safety and Effectiveness Results through 12 months

	TAXUS (N=662)	Control (N=652)	Difference [95% CI]	P
Effectiveness Measures				
Clinical Procedural Success	97.3% (643/661)	97.4% (635/652)	-0.1% [-1.9%, 1.6%]	1.0000
Technical Success	97.9% (648/ 661)	98.2% (640/ 652)	-0.3% [-1.8%, 1.2%]	0.8436
9 Month Results				
[2]Target Vessel Revascularization	4.7% (31/655)	12.1% (78/ 645)	-7.4% [-10.4%, -4.4%]	<0.0001
In-stent restenosis	5.5% (16/ 291)	24.4% (65/ 266)	-18.9% [-24.7%,-13.1%]	<0.0001
Analysis segment restenosis	7.9% (23/ 291)	26.6% (71/ 267)	-18.7% [-24.8%,-12.5%]	<0.0001
MLD (mm), In-stent				
Post-Procedure	2.65 +/- 0.42 (373)	2.67 +/- 0.41 (351)	-0.01 [-0.07,0.05]	0.6577
9-Month	2.26 +/- 0.58 (291)	1.75 +/- 0.65 (266)	0.51 [0.41,0.61]	<0.0001
MLD (mm), Analysis Segment				
Post Procedure	2.26 +/- 0.48 (374)	2.29 +/- 0.50 (356)	-0.03 [-0.10,0.04]	0.4526
9-Month	2.03 +/- 0.55 (291)	1.68 +/- 0.61 (267)	0.35 [0.26, 0.45]	<0.0001
% DS, In-stent				
Post Procedure	4.21 +/- 10.84 (373)	5.16 +/- 11.41 (351)	-0.95 [-2.57, 0.67]	0.2497
9-Month	17.43 +/-17.71 (291)	37.24 +/- 19.76 (266)	-19.82 [-22.93,16.70]	<0.0001
% DS, Analysis Segment				
Post Procedure	19.16 +/- 9.67 (374)	19.33 +/- 10.45 (356)	-0.17 [-1.63, 1.29]	0.8219
9-Month	26.29 +/- 15.45 (291)	39.79 +/- 18.45 (267)	-13.50 [-16.31,-10.68]	<0.0001
Late Loss, In-stent (mm)	0.39 +/- 0.50 (291)	0.92 +/- 0.58 (266)	-0.53 [-0.62, -0.44]	<0.0001
Late Loss, Analysis Segment (mm)	0.23 +/- 0.44 (291)	0.61 +/- 0.57 (267)	-0.38 [-0.47, -0.30]	<0.0001
% Net Volume Obstruction	12.20 +/- 12.44 (81)	29.40 +/- 14.05 (80)	-17.19 [-21.29,-13.10]	<0.0001
Minimum Lumen Area	5.14 +/- 2.19 (81)	4.15 +/- 1.64 (80)	0.99 [0.39, 1.59]	0.0014
Neointimal Volume	17.56 +/- 18.21 (81)	41.48 +/- 23.02 (80)	-23.92 [-30.33,-17.51]	<0.0001
Clinical Endpoints to 9 months				
[1]TVR-Free	95.25%	87.89%	7.36% [4.35%, 10.37%]	<0.0001
[1]TLR-Free	96.93%	88.51%	8.42% [5.62%, 11.22%]	<0.0001
[1]TVF-Free	92.40%	85.48%	6.92% [3.54%, 10.30%]	0.0001
[1]MACE-Free	91.51%	84.88%	6.63% [3.14%, 10.12%]	0.0003
Clinical Endpoints to 12 months				
[1]TVR-Free	92.87%	82.88%	9.99% [6.41%, 13.57%]	<0.0001
[1]TLR-Free	95.58%	84.89%	10.69% [7.46%, 13.92%]	<0.0001
[1]TVF-Free	90.03%	80.57%	9.46% [5.61%, 13.31%]	<0.0001
[1]MACE-Free	89.15%	79.97%	9.18% [5.26%, 13.10%]	<0.0001
[2]**Safety Measures**				
In-hospital MACE	2.4% (16/662)	2.1% (14/ 652)	0.3% [-1.3%, 1.9%]	0.854
MACE to 9 months	8.5% (56/ 655)	15.2% (98/ 645)	-6.6% [-10.1%, -3.1%	0.0002
MACE to 12 months	10.7% (70/ 653)	20.0% (129/ 644)	-9.3% [-13.2%, -5.4%]	<0.0001
TVR to 9 months (Primary Endpoint)	4.7% (31/ 655)	12.1% (78/ 645)	-7.4% [-10.4%, -4.4%]	<0.0001
TVR to 12 months	6.9% (45/ 653)	16.9% (109/ 644)	-10.0% [-13.5%, -6.5%]	<0.0001
TVF to 9-months	7.6% (50/655)	14 6% (94/645)	-6.9% [-10.3%, -3.5%]	0.0001
TVF to 12-months	9.7% (64/ 653)	19.2% (125/ 644)	-9.6% [-13.4%, -5.8%]	<0.0001
Stent Thrombosis to 30 days	0.3% (2/ 662)	0.6% (4/ 652)	-0.3% [-1.0%, 0.4%]	0.4487
Stent Thrombosis to 9 months	0.6% (4/ 655)	0.8% (5/ 645)	-0.2% [-1.1%, 0.7%]	0.7513
Stent Thrombosis to 12 months	0.6% (4/ 653)	0.8% (5/ 644)	-0.2% [-1.1%, 0.7%]	0.7515
CVA to 12 months	1.7% (11/ 654)	0.8% (5/ 644)	0.9% [-0.3%, 2.1%]	0.2075
Serious Bleeding Events to 12 months	2.8% (18/654)	1.9% (12/644)	0.9% [-0.7%, 2.5%]	0.3564
Serious Vascular Events to 12 months	1.8% (12/653)	1.9% (12/644)	-0.0% [-1.5%, 1.4%]	1.0000
Platelet Disorders to 12 months	0.6% (4/653)	0.8% (5/644)	-0.2% [-1.1%, 0.7%]	0.7515
Hematological Dyscrasia to 12 months	1 5% (10/654)	0 8% (5/644)	0.7% [-0.4%, 1.9%]	0.2991

Numbers are % (Count/Sample Size) or Mean±SD (N) (Min, Max). CI = Confidence Interval.
Difference = TAXUS SR – Control.
SE of Difference: = $\text{sqrt}(p_1q_1/n_1+p_2q_2/n_2)$ for proportions, = $\text{sqrt}[(1/n_1 + 1/n_2)\{(n_1-1)s_1^2 + (n_2-1)s_2^2\}/(N-2)]$ for continuous variables.
95% CI of Difference = Diff±1.96·SE. 95%

P-values are two-sided and from Student's t test for continuous variables and Fisher's exact test for discrete variables
Undef = Undefined.
Primary endpoint is 9-month TVR.
Clinical Procedural Success: using the assigned study stent to achieve an in-target-lesion diameter stenosis <30% in the average of 2 near- orthogonal projections, as visually assessed by the physician, without the occurrence of in-hospital MACE.
Technical success: successful delivery and deployment of the study stent to the target lesion, without balloon rupture, embolization, or use of the product outside the treatment strategy.
MLD = Minimum Lumen Diameter
WHO-defined non-Q-wave MI – Elevation of post-procedure CK levels to >2 times normal with elevated CKMB in the absence of new pathological Q-waves.
Stent thrombosis:
Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis
Angiographic documentation of a complete occlusion (TIMI flow 0 or 1) of a previously successfully treated artery (TIMI flow 2 to 3 immediately after stent placement and DS ≤30%), and/or angiographic documentation of a flow limiting thrombus within or adjacent to a previously successfully treated lesion
Acute MI of the distribution of the treated vessel
Death within first 30 days (without other obvious cause) was considered a surrogate for stent thrombosis when angiography was not available
CVA – Sudden onset of vertigo, numbness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persisted >24 hours.
9-Month MACE: the proportion of patients who experience a MACE up to the 9-month follow-up. MACE includes cardiac death, myocardial infarction (MI) including WHO defined Q- and non-Q-wave MI, and target vessel revascularization (TVR).
30-Day MACE: binary MACE rate to 30 days post-procedure.
9-Month Restenosis: the proportion of patients who demonstrate ≥50% diameter stenosis of the target lesion by Quantitative Coronary Analysis (QCA) performed at the Angiographic Core Laboratory at the 9-month follow-up.
Serious Bleeding Complications included: hemorrhage (gastric ulcer, mediastinal, rectal, upper GI, and GI not specified), hematuria, hemoptysis, and hemothorax. Serious Vascular Complications included: hematoma (catheter site and not specified), hemorrhage (catheter site and retroperitoneal), arterial injury, and vascular pseudoaneurysm. Platelet disorders included thrombocytopenia. Hematologic dyscrasia included: anemia, and pancytopenia.
The following survival estimates are by Kaplan-Meier Methods with standard error estimates by Greenwood formula:
†TLR-Free– No target lesion revascularization.
†TVR-Free – No target vessel revascularization.
†TVF-Free – No cardiac death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.
†MACE-Free – No death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.
[2] For each parameter in the safety measures, the denominator is the number of patients randomized to each treatment arm (excluding de-registered patients) who had sufficient follow up (at least 240 days for 9 month visit and at least 330 days for 12 month visit) plus any patients who had an event prior to the milestone visit.

Figure 3.TAXUS IV Freedom From TVR to 1 Year (Event-Free Survival ± 1.5 SE)



Time After Initial Procedure

TAXUS	0	7	14	30	60	90	120	150	180	270	365
Entered	662	662	660	660	660	656	652	646	641	633	615
Censored	0	2	0	0	1	1	1	4	3	4	330
Events	0	0	0	0	3	3	5	1	5	14	14
At Risk	662	661	660	660	659.5	655.5	651.5	644	639.5	631	450
Events/Month	0.0	0.0	0.0	0.0	3.0	3.0	5.0	1.0	5.0	4.7	4.4
Event Free	100.0%	100.0%	100.0%	100.0%	99.5%	99.1%	98.3%	98.2%	97.4%	95.2%	92.9%
Std Error	0.00%	0.00%	0.00%	0.00%	0.26%	0.37%	0.50%	0.52%	0.62%	0.83%	1.04%

Control	0	7	14	30	60	90	120	150	180	270	365
Entered	652	652	650	650	648	646	631	616	597	586	562
Censored	0	1	0	1	0	2	2	4	1	1	274
Events	0	1	0	1	2	13	13	15	10	23	31
At Risk	652	651.5	650	649.5	646	645	630	614	596.5	585.5	425
Events/Month	0.0	4.3	0.0	1.9	2.0	13.0	13.0	15.0	10.0	7.7	9.8
Event Free	100.0%	99.8%	99.8%	99.7%	99.4%	97.4%	95.4%	93.0%	91.5%	87.9%	82.9%
Std Error	0.00%	0.15%	0.15%	0.22%	0.31%	0.63%	0.82%	1.00%	1.10%	1.29%	1.50%

Tests Between Groups, To 365 Days

Test	Chi-Square	Degrees of Freedom	p-Value
Log-Rank	31.5258	1	<0.0001
Wilcoxon	32.3772	1	<0.0001

Patients event-free at 366 days or later are censored at 366 days.
Intervals are end inclusive, e.g. interval 90 is defined as 31-90 days, inclusive.
Event-free and standard error estimates are for interval end. Standard errors by Greenwood formula.
"at risk" is the number of patients who "entered" an interval minus (the number of patients "censored" during the interval divided by 2).
"censored" is the number of patients whose last follow-up occurred during that interval and did not have a TVR, e.g., a patient who did not have a TVR and whose last follow-up was on Day 178 would be censored in the 151-180 interval (180 column).

B. TAXUS II (SR) Supporting Clinical Trial

Objective: The primary objective of this study was to evaluate the safety and effectiveness of the TAXUS™ NIRx™ Paclitaxel-Eluting Coronary Stent System (1 μg/mm^2 SR formulation) compared with a matched uncoated control stent.

Conclusion: In selected patients, use of the SR formulation of the TAXUS NIRx (SR) Stent significantly reduced the percent of in-stent net volume obstruction as determined by IVUS at 6 months. There were significant improvements in overall MACE rates as well as reintervention procedures required in the target lesion. No substantial differences were observed as compared to the uncoated control group with respect to safety assessments.

Design: This was a prospective, double-blind trial conducted at 38 sites in 15 countries. Eligible patients had documented angina pectoris and a single *de novo* lesion in a native coronary artery measuring ≤ 12 mm in length with a visual RVD ≥ 3.0 mm and ≤ 3.5 mm.

A total of 267 patients were enrolled and evaluable in this study: 131 TAXUS group and 136 in the Control group. Patients were randomized to receive either a TAXUS NIRx™ (SR) Stent or uncoated NIR coronary stent (bare metal control). After the procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for 6 months.

Follow-up included 1, 6, and 12 month clinical assessments. In addition, patients agreed to annual telephone follow-up for MACE clinical parameters through 5 years post procedure. Follow-up through 12 months (± 30 days) is currently available for 264/267 (98.8%) of patients.

All patients were required to have angiographic and IVUS follow-up at 6 and 24 months. Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and also for the area within the stent margins, including the area immediately 5 mm proximal and distal from the stent margins (analysis segment).

Demographics: There were no clinically significant differences between groups with respect to baseline demographics or clinical characteristics. Factors evaluated included age (mean 61 years), gender (74.5% male), diabetes (13.5%), prior MI (38.5%), hypertension (65%), LAD (42%), LCX (19%), RCA (39%), RVD (mean 2.7 mm), MLD (mean 1.0 mm), %DS (mean ~63%), current smoking (21.4%), IIb/IIIa use (12%) and lesion length (mean 10.5 mm). Demographic data regarding hyperlipidemia, ethnicity and ejection fraction were not monitored in this study. A statistically significantly higher CCS Class was noted in the uncoated control group as compared to the TAXUS group

(*P*=0.0104). This was due to a difference in CCS Class II (42.7% TAXUS vs. 27.9% Control) and CSS Class III (7.6% TAXUS vs. 19.9% Control). CCS Class I, and CCS Class IV were comparable between treatment groups. The difference in CCS class was not found to be a significant predictor of outcome in the trial.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by coordinators at the clinical sites. Angiographic and IVUS outcomes were assessed in a blinded fashion by quantitative analysis at designated core laboratories. An independent Clinical Events Committee adjudicated clinical events, and the trial was monitored by an independent Data Monitoring Committee.

Results: In selected patients, 6-month percent in-stent net volume obstruction (primary endpoint) as determined by IVUS was statistically significantly lower in the TAXUS™ NIRx™ (SR) Stent treatment group as compared with the uncoated control group (7.85% versus 23.17%, $p<0.0001$).

In-stent restenosis, for the TAXUS NIRx (SR) Stent treatment group was 2.3% as compared to 17.9% for the uncoated control group ($p<0.0001$). Analysis segment restenosis, was 5.5% for the TAXUS NIRx (SR) Stent group as compared to 20.1% for the uncoated control group ($p=0.0004$). At the 6-month time-point, statistically significant improvements were also observed in late loss, MLD, and %DS for the TAXUS NIRx (SR) Stent group as compared to the uncoated control group.

Lower rates for MACE were observed in the TAXUS NIRx (SR) Stent group as compared with the uncoated control group at 6-months follow-up (8.5% versus 19.5%, $p=0.0125$), and 12-month follow-up (10.9% versus 22.0%, $p=0.0191$) (**Table 12**). MACE-free survival was improved in the TAXUS group as compared with the uncoated control group at both 6 and 12 months.

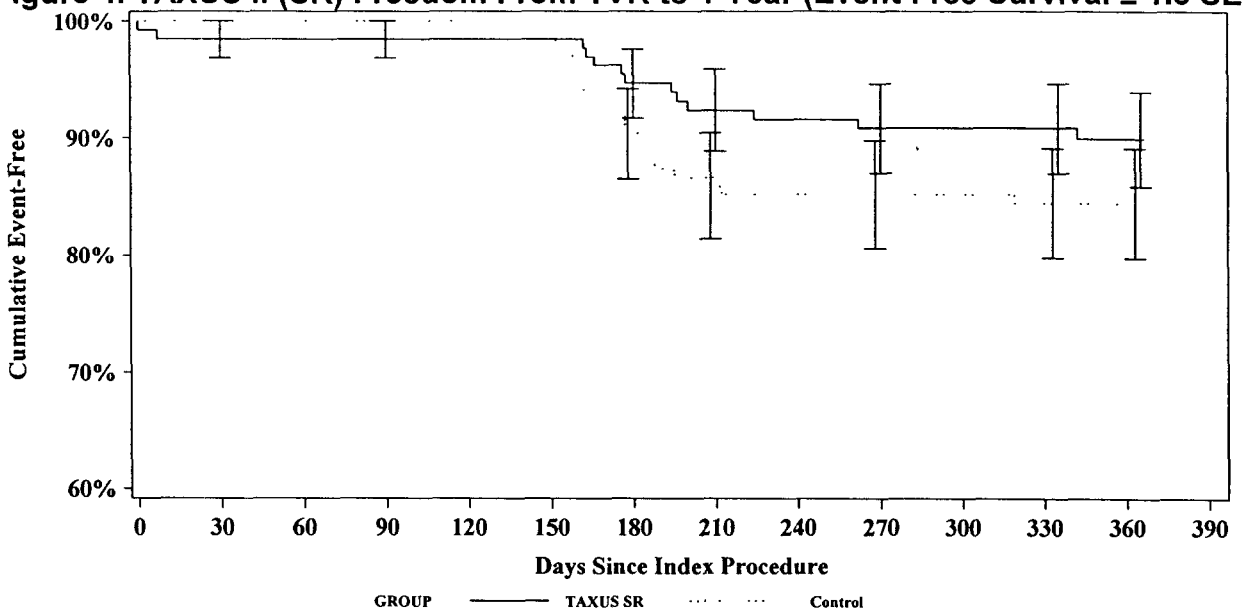
Table 12 summarizes the principle safety and effectiveness results of the TAXUS II (SR) trial through 12 months. **Figure 4** provides the cumulative percent of patients who are TVR-Free through 12 months.

Table 12. TAXUS II (SR) Principal Safety and Effectiveness Results through 12 months

	TAXUS II (SR) (N=131)	Control (N=136)	Difference [95% CI]	P Value
Effectiveness Measures				
Clinical Procedural Success	95.4% (125/131)	93.4% (127/136)	2.0% [-3.5%, 7.5%]	0.5976
Technical Success	97.7% (128/131)	98.5% (134/136)	-0.8% [-4.1%, 2.4%]	0.6794
6-Month % Net Volume Obstruction	7.85±9.87 (118)	23.17±18.19 (125)	-15.32 [-19.03, -11.61]	<0.0001
6-month In-stent restenosis	2.3% (3/128)	17.9% (24/134)	-15.6% [-22.6%, -8.6%]	<0.0001
6-month Analysis segment restenosis	5.5% (7/128)	20.1% (27/134)	-14.7% [-22.5%, -6.8%]	0.0004
MLD (mm), Stented Segment				
Post-Procedure	2.53±0.29 (128)	2.58±0.37 (135)	-0.05 [-0.13, 0.03]	0.2132
6-Month	2.23±0.47 (128)	1.79±0.54 (134)	0.44 [0.32, 0.56]	<0.0001
MLD (mm), Analysis Segment				
Post Procedure	2.15±0.37 (128)	2.23±0.43 (135)	-0.08 [-0.17, 0.02]	0.1202
6-Month	2.01±0.46 (128)	1.70±0.49 (134)	0.31 [0.20, 0.43]	<0.0001
% DS, Stented Segment				
Post Procedure	10.90±6.52 (128)	10.20±5.94 (135)	0.70 [-0.81, 2.20]	0.3659
6-Month	19.53±12.71 (128)	31.77±17.11 (134)	-12.25 [-15.91, -8.59]	<0.0001
% DS, Analysis Segment				
Post Procedure	23.07±9.27 (128)	21.24±8.41 (135)	1.83 [-0.31, 3.97]	0.0943
6-Month	26.79±12.78 (128)	35.11±15.09 (134)	-8.32 [-11.71, -4.93]	<0.0001
6-Month Late Loss (mm), Stented Segment	0.31±0.38 (127)	0.79±0.45 (134)	-0.48 [-0.58, -0.38]	<0.0001
TLR Free to 12 months	95.4%	87.5%	7.9% [1.3%, 14.5%]	0.0279
TVR Free to 12 months	90.1%	84.6%	5.5% [-2.4%, 13.5%]	0.2013
MACE free to 12 months	89.3%	78.7%	10.6% [2.0%, 19.3%]	0.0201
[1]**Safety Measures**				
In-Hospital MACE	1.5% (2/131)	4.4% (6/136)	-2.9% [-6.9%, 1.2%]	0.2823
MACE to 30 days	2.3% (3/131)	4.4% (6/136)	-2.1% [-6.4%, 2.2%]	0.5010
MACE to 6 months	8.5% (11/130)	19.5% (26/133)	-11.1% [-19.4%, -2.8%]	0.0125
MACE to 12 months	10.9% (14/129)	22.0% (29/132)	-11.1% [-20.0%, -2.2%]	0.0191
Stent Thrombosis to 1 day	0.8% (1/131)	0.0% (0/136)	0.8% [-3.8%, 7.4%]	0.4906
Stent Thrombosis to 6 months	0.8% (1/130)	0.0% (0/133)	0.8% [-3.9%, 7.4%]	0.4906
Stent Thrombosis to 12 months	1.6% (2/129)	0.0% (0/132)	1.5% [-3.4%, 9.0%]	0.2398
Serious Bleeding Events to 12 months	3.9% (5/129)	6.0% (8/133)	-2.1% [-7.4%, 3.1%]	0.5718
Serious Vascular Events to 12 months	3.1% (4/129)	0.8% (1/132)	2.3% [-1.0%, 5.7%]	0.2098

Numbers are % (Count/Sample Size) or Mean±SD (N) (Min, Max). CI = Confidence Interval.
Difference = TAXUS SR stent – Control.
SE of Difference: = $\text{sqrt}(p_1q_1/n_1+p_2q_2/n_2)$ for proportions, = $\text{sqrt}[(1/n_1 + 1/n_2)\{(n_1-1)s_1^2 + (n_2-1)s_2^2\}/(N-2)]$ for continuous variables.
95% CI of Difference = Diff±1.96·SE. 95% for all measures except stent thrombosis where exact confidence intervals were calculated due to one group having a rate of zero
P-values are two-sided and from Student's t test for continuous variables and Fisher's exact test for discrete variables.
Primary endpoint is 6-Month Percent Stented Segment Net Volume Obstruction, determined by IVUS.
Event/success rates are number of patients with the outcome ÷ the number of patients evaluable for the outcome.
Clinical Procedural Success: using the assigned study product to achieve an in-target-lesion diameter stenosis <30% in the average of 2 near-orthogonal projections, as visually assessed by the physician, without the occurrence of in-hospital MACE.
6-Month MACE: the proportion of patients who experience a MACE up to the 6-month follow-up. MACE includes cardiac death, myocardial infarction (MI) including Q- and non-Q-wave MI, and target vessel revascularization (TVR).
30-Day MACE: binary MACE rate to 30 days post-procedure
12-Month MACE: binary MACE rate to 365 days post-procedure.
6-Month Restenosis: the proportion of patients who demonstrate ≥50% diameter stenosis of the target lesion by Quantitative Coronary Analysis (QCA) performed at the Angiographic Core Laboratory at the 6-month follow-up.
[1] For each parameter in the safety measures, the denominator is the number of patients randomized to each treatment arm who had sufficient follow up (at least 150 days for 6 month visit and at least 335 days for 12 month visit) plus any patients who had an event prior to the milestone visit.

Figure 4. TAXUS II (SR) Freedom From TVR to 1 Year (Event-Free Survival ± 1.5 SE)



Time After Initial Procedure

TAXUS SR	0	14	30	90	180	210	270	335	365
Entered	131	130	129	129	129	124	120	118	113
Censored	0	0	0	0	0	1	0	5	69
Events	1	1	0	0	5	3	2	0	1
At Risk	131	130	129	129	129	123.5	120	115.5	78.5
Events/Month	30.0	2.1	0.0	0.0	1.7	3.0	1.0	0.0	1.0
Event Free	99.2 %	98.5 %	98.5 %	98.5 %	94.7 %	92.3 %	90.8 %	90.8 %	89.9 %
Std Error	0.8%	1.1%	1.1%	1.1%	2.0%	2.3%	2.5%	2.5%	2.7%

Control	0	14	30	90	180	210	270	335	365
Entered	136	136	135	135	135	122	115	114	107
Censored	0	1	0	0	0	1	0	6	54
Events	0	0	0	0	13	6	1	1	0
At Risk	136	135.5	135	135	135	121.5	115	111	80
Events/Month	0.0	0.0	0.0	0.0	4.3	6.0	0.5	0.5	0.0
Event Free	100%	100%	100%	100%	90.4 %	85.9 %	85.2 %	84.4 %	84.4 %
Std Error	0.0%	0.0%	0.0%	0.0%	2.5%	3.0%	3.1%	3.1%	3.1%

Tests Between Groups, To 365 Days

Test	Chi-Square	Degrees of Freedom	p-Value
Log-Rank	1.945	1	0.163
Wilcoxon	2.093	1	0.148

Patients event-free at 366 days or later are censored at 366 days.
Intervals are end inclusive, e.g. interval 90 is defined as 31-90 days, inclusive.
Event-free and standard error estimates are for interval end. Standard errors by Greenwood formula.
"at risk" is the number of patients who "entered" an interval minus (the number of patients "censored" during the interval divided by 2).
"censored" is the number of patients whose last follow-up occurred during the interval and did not have a TVR, e.g., a patient who did not have a TVR and whose last follow-up was on Day 178 would be censored in the 151-180 interval (180 column).

C. TAXUS I Feasibility Clinical Trial

Objective: The primary objective of this study was to evaluate the safety at 30 days (MACE) of the TAXUS™ NIRx™ Paclitaxel-Eluting Coronary Stent System (1 µg /mm^2 SR formulation), as compared with a matched uncoated control stent. Secondary objectives included QCA and IVUS evaluation at 6 months.

Conclusion: In selected patients, use of the TAXUS NIRx (SR) Stent provided favorable MACE, QCA, and IVUS results through 24 months of follow-up.

Design: This was a multi-center, prospective, randomized, double-blind study. Eligible patients were those presenting for stenting of *de novo* or restenotic lesions of a native coronary artery (RVD 3.0 to 3.5 mm) with a target lesion ≤12 mm in length and stenosis between 50% and 99% in diameter, using visual estimates, who were candidates for PCI and CABG, and had documented angina pectoris or functional ischemia.

A total of 61 patients were enrolled and evaluable in this study: 31 in the TAXUS group and 30 in the Control group. Patients were randomized to receive either a paclitaxel-eluting TAXUS NIRx (SR) Stent or an uncoated NIRx coronary stent (bare metal control). After the procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for 6 months.

Follow-up included 1, 6, 9, 12 months, and 2 year clinical assessments. In addition, patients agreed to annual telephone follow-up for clinical parameters through 5 years post-procedure. Clinical follow-up is available through 2 years.

Angiography and IVUS were performed at the 6-month follow-up visit for all patients.

Demographics: Patients were well matched for baseline demographics with no statistically significant differences between groups ($p>0.05$). Factors evaluated included age (mean 65 years), gender (89% male), diabetes (18%), prior MI (28%), hypertension (61%), hyperlipidemia (74%), smoking history (49%), LAD (41%), LCX (29.5%), RCA (29.5%), RVD (mean 2.97 mm), MLD (mean 1.27 mm), %DS (mean 57%), and lesion length (mean 11.28 mm). Demographic data regarding hyperlipidemia, smoking history, IIb/IIIa use, ethnicity and ejection fraction were not monitored in this study. There were more patients with CSS Class II in the TAXUS group (61.3% TAXUS vs. 33.3% Control) and more patients with CSS Class III and IV in the control group (25.8% TAXUS vs. 36.6% Control) though none of the differences were statistically significant. The difference in CCS class was not found to be a significant predictor of outcome in the trial.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by coordinators at the clinical sites.

Angiographic and IVUS outcomes were assessed in a blinded fashion by quantitative analysis at designated core laboratories. An independent Clinical Events Committee adjudicated clinical events.

Results: The primary endpoint, the 30-day MACE rate, was zero in both groups. The cumulative MACE rate in the TAXUS group at 12 months was 3% (1/31) and in the Control group was 10% (3/30). No additional MACE events were reported in either the TAXUS NIRx (SR) Stent treatment group or control group at two years.

In-stent improvements were noted in MLD, late lumen loss and loss index.

Table 13 summarizes the principle safety and effectiveness results of the TAXUS I trial through 2 years.

Table 13. TAXUS I Principal Safety and Effectiveness Results Through 2 Years

Safety Measures and Other Clinical Events	TAXUS NIRx™ (SR) N=31	NIR™ Control N=30	*p-value*
MACE (30-day)	0% (0/31)	0% (0/30)	NA
Cardiac Death	0% (0/31)	0% (0/30)	NA
Q-Wave MI	0% (0/31)	0% (0/30)	NA
TVR (CABG and/or PCI)	0% (0/31)	0% (0/30)	NA
MACE (12-Month)	3% (1/31)	10% (3/30)	0.612
Cardiac Death	0% (0/31)	0% (0/30)	NA
Q-Wave MI	0% (0/31)	0% (0/30)	NA
TVR (CABG and/or PCI)	3% (1/31)	10% (3/30)	0.612
MACE (2-Year)	3% (1/31)	10% (3/30)	0.612
Cardiac Death	0% (0/31)	0% (0/30)	NA
Q-Wave MI	0% (0/31)	0% (0/30)	NA
TVR (CABG and/or PCI)	3% (1/31)	10% (3/30)	0.612
Stent Thrombosis to 2 years	0% (0/31)	0% (0/31)	NA
QCA In-Stent Lesion Characteristics			
Pre-procedure			
RVD, mm	2.99±0.46 (31)	2.94±0.52 (29)	0.699
MLD, mm	1.30±0.43 (31)	1.23±0.43 (29)	0.558
%DS	56.51±12.26 (31)	57.82±13.24 (29)	0.692
Lesion length, mm	10.70±3.27 (31)	11.89±4.93 (29)	0.272
Post-procedure			
MLD, mm			0.414
%DS	6.12±9.49 (31)	2.95±0.34 (31)	0.096
6-Month follow-up			
RVD, mm	3.02±0.47 (30)	3.01±0.53 (29)	0.899
MLD, mm	2.60±0.49 (30)	2.19±0.65 (29)	0.008
%DS	13.56±11.77 (30)	27.23±16.69 (29)	<0.001
Restenosis Rate ≥50%	0% (0/30)	10% (3/29)	0.112
Late lumen loss, mm	0.36±0.48 (30)	0.71±0.47 (26)	0.009
Loss index	0.22±0.29 (30)	0.45±0.29 (26)	0.004

Numbers are % (Count/Sample Size) or Mean±SD (N).
P-values are two-sided and from Student's t test for continuous variables and Fisher's exact test for discrete variables.
Primary endpoint is 30-day MACE.
Event/success rates are number of patients with the outcome ÷ the number of patients evaluable for the outcome.
MLD = Minimum Lumen Diameter
RVD = Reference Vessel Diameter
% DS = Percent diameter stenosis
MACE includes cardiac death, myocardial infarction (MI) including Q- and non-Q-wave MI, and target vessel revascularization (TVR).binary MACE rate to 30 days post-procedure
MACE (30-day): the proportion of patients who experience a MACE up 30 days post-procedure
MACE (6-Months): the proportion of patients who experience a MACE up to 6 months post-procedure
MACE (12-month): the proportion of patients who experience a MACE up to 12 months post-procedure
MACE (2-year): the proportion of patients who experience a MACE up to 2 years post-procedure
Restenosis rate: the proportion of patients who demonstrate ≥50% diameter stenosis of the target lesion by Quantitative Coronary Analysis (QCA) performed at the Angiographic Core Laboratory at the 6-month follow-up.

D. Gender Bias

The gender selection in this series of clinical trials was completely random, and solely based upon exclusion and inclusion criteria. In the TAXUS IV pivotal trial (conducted in the US), men represented 72% of the population. In the TAXUS II supporting trial (conducted outside of the US), men represented 74.5% of the population. In the TAXUS I feasibility trial (conducted outside of the US), men represented 89% of the population. The ratio of men versus women in each of these trials is reflective of the underlying distribution of the disease for the given

age groups, ethnic groups and stages of disease in these populations. No selection bias on the basis of gender was identified during the review. In addition, no differences in safety or effectiveness were found, with respect to gender.

XII. CONCLUSIONS DRAWN FROM THE STUDIES

The safety and effectiveness of the TAXUS Express² Paclitaxel-Eluting Coronary Stent System is based on the results obtained from biocompatibility; *in vivo* pharmacokinetics; *in vitro* engineering testing; coating characterization; chemistry, manufacturing and controls information; *in vivo* animal testing; sterilization and stability testing; and clinical studies. These test results revealed the following:

The biocompatibility, *in vivo* pharmacokinetics, and *in vivo* animal testing that were conducted demonstrated that the acute and chronic *in vivo* performance characteristics of the product are safe and acceptable for clinical use.

The *in vitro* engineering testing conducted on the stent and delivery system(s) demonstrated that the performance characteristics met the product specifications and the coating characterization testing adequately described the important attributes of the paclitaxel/polymer coating. The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released.

The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 6 months.

The clinical testing conducted demonstrated that the product provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the instructions for use.

XIII. PANEL RECOMMENDATION

At an advisory meeting held on November 20, 2003, the Circulatory System Devices Panel recommended that Boston Scientific's PMA for the TAXUS Express² Paclitaxel-Eluting Coronary Stent System (Monorail and Over-the-Wire) be approved subject to submission to, and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

(1) The labeling should specify that patients should receive an antiplatelet regimen of aspirin and clopidogrel or ticlopidine for 6 months following receipt of the stent.

(2) The labeling should state that the interaction between the TAXUS Express Stent and stents that elute other compounds has not been studied.

(3) The labeling should state the maximum permissible inflation diameter for the TAXUS Express Stent.

(4) The numbers in the tables in the instructions for use that report primary effectiveness endpoints should be corrected to reflect the appropriate denominators.

(5) The labeling should include the comparator term "bare metal Express stent" in the indications.

XIV. CDRH DECISION

CDRH concurred with the Panel's first four recommendations of November 20, 2003, and Boston Scientific revised the labeling accordingly and submitted updates in various PMA amendments. The final panel recommendation of November 20, 2003, was to revise the labeling to include the comparator term "bare metal Express stent" in the indications. This was based on the Panel's recommendation that an indicated claim for reducing restenosis would be acceptable, if accompanied by identification of the comparison stent studied. The Agency considered this recommendation, and on February 5, 2004, FDA notified Boston Scientific that while FDA agrees with the Circulatory System Devices Panel that the results of the Taxus IV study demonstrated that the TAXUS Stent System did reduce restenosis when compared to identical uncoated Express control stents, FDA does not agree that this information is appropriate for inclusion in the indication statement. More specifically, the indication is intended to reflect the use of the product as a whole in a particular patient population (i.e., to improve luminal diameter in patients with de novo lesions of a certain size). The fact that this stent system results in better outcomes with respect to reducing restenosis when compared to other alternatives (uncoated Express stent) should be reflected in the clinical trials section of the DFU.

During the deliberations, the Panel was asked to consider issues regarding the animal study data. The pathology findings from the animal studies submitted in the application noted endothelial coverage of the stent, no structural deterioration of the coronary artery wall, and an absence of thrombus, which corresponded with the clinical findings from TAXUS I, II and IV. However, the animal studies also revealed marked histologic changes in the media (i.e., smooth muscle cell loss, ingrowth of fibrous tissue, neovascularization, dystrophic calcification) in the vessel wall. In addition, parastrut amorphous material or "PAM" was noted. These findings were more pronounced in the MR formulation versus the SR formulation that was proposed for commercialization. The degree of response appeared to correlate with increasing dose, with the least response occurring in the animals implanted with the SR formulation. These findings were present at all time points, including 180 and 360 days, but appeared to be resolving over time, and did not result in structural deterioration of the coronary wall. The Panel recommended that the clinical data

provided was sufficient to address potential concerns raised by the animal studies. CDRH concurred with this recommendation.

Additionally, one of the Panel members at this meeting identified a concern with drug interactions that could impact on the delivery of paclitaxel from the TAXUS Express Stent to the tissue immediately adjacent to the stent. The labeling was revised in a PMA amendment to state: "Formal drug interaction studies have not been conducted with the TAXUS Express Stent. Consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place a TAXUS Express Stent in a patient who is taking a drug with known interactions to paclitaxel or when deciding to initiate therapy with such a drug in a patient that has recently received a TAXUS Express Stent."

The applicant's manufacturing and sterilization facilities were inspected on the following dates:

- July 7, 2002 (Plymouth, MN)
- July 31, 2002 (Coventry, RI)
- August 26, 2002 (Quincy, MA)
- September 11, 2003 (Tullamore, Ireland)
- September 17, 2003 (Beek, The Netherlands)
- January 9, 2004 (Galway, Ireland)
- February 5, 2004 (Maple Grove, MN)

The inspections found these facilities to be in compliance with relevant device Good Manufacturing Practice (GMP) regulations and pharmaceutical current Good Manufacturing Practice (cGMP) regulations.

FDA issued an approval order on March 4, 2004.

XV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.